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Improved retroviral vectors for hematopoietic stem cell protection and in vivo selection.**Baum C, Eckert HG, Stockschrader M, Just U, Hegewisch-Becker S, Hildinger M, Uhde A, John J, Ostertag W.**

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Therapeutic gene transfer into hematopoietic cells is critically dependent on the evolution of methods that allow ex vivo expansion, high-frequency transduction, and selection of gene-modified long-term repopulating cells. Progress in this area needs elaboration of defined culture and transduction conditions for long-term repopulating cells and improvement of gene transfer systems. We have optimized retroviral vector constructions based on murine leukemia viruses (MuLV) to overcome the transcriptional repression encountered with the use of conventional Moloney MuLV (MoMuLV) vectors in early hematopoietic progenitor cells (HPC). Novel retroviral vectors, termed FMEV (for Friend-MCF/MESV hybrid vectors), were cloned that mediate greatly improved gene expression in the myeloerythroid compartment. Transfer of the selectable marker multidrug resistance 1 (mdr1), FMEV, in contrast to conventional MoMuLV-related vectors currently in use for clinical protocols, mediated background-free selectability of transduced human HPC in the presence of myeloablative doses of the cytostatic agent paclitaxel in vitro. Furthermore, FMEV also greatly improved chemo-protection of hematopoietic progenitor cells in a murine model system in vivo. Finally, when a second gene was transferred along with mdr1 in an FMEV-backbone, close to 100% coexpression was observed in multidrug-resistant colonies. These observations have significant consequences for a number of ongoing and planned gene therapy trials, for example, stem cell protection to reduce the myelotoxic side effects of anticancer chemotherapy, correction of inherited disorders involving hematopoietic cells, and antagonism of HIV infection.

Publication Types:

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